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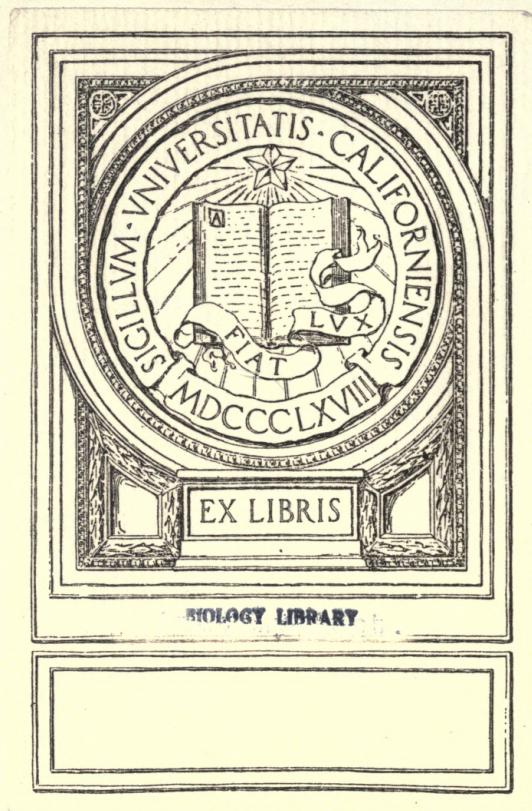
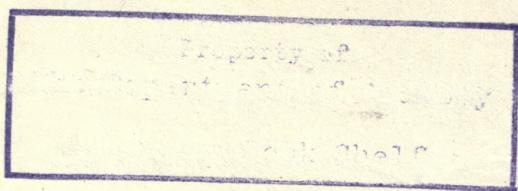
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The Normal Mode of Secretion in the Thyroid Gland

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From the Hull Laboratory of Anatomy, University
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THE NORMAL MODE OF SECRETION IN THE THYROID GLAND

R. R. BENSLEY.

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ONE PLATE IN COLOR

In the glands of the alimentary canal the process of secretion is associated with definite changes in the structure of the secreting cells, and with the accumulation in them of products, granular or otherwise, which may be interpreted as the organic antecedents of the secretion itself. Even in some of the internal secreting glands, as, for example, the islets of Langerhans of the pancreas, functioning is associated with the storage or exhaustion of intracellular products which may be similarly interpreted. By means of these secretion antecedents an observer, who has, by experiment and observation, acquainted himself with the secretory mode, may form an estimate of the secretory potential at the time of observation.

In the thyroid gland, on the other hand, the search for such evidences of secretory activity, has been, as regards the nature of the intracellular secretion antecedents, of so contradictory a nature, and of such doubtful functional import, that, at present, we are unable to state from the examination of a thyroid gland whether the gland was active or inactive. Accordingly, different observers, as, for example, in Grave's disease, in discussing the same results, have arrived at diametrically opposed conclusions.

One of the features of the thyroid gland, in particular, which baffled interpretation was the presence in it of a storage product, the so-called colloid, the route and rate of resorption of which have remained problematical, though chemical and physiological studies indicated that it contained the physiologically active

thyroid substances. Some observers have even doubted the resorption of this material, and have suggested that the function of the thyroid gland was primarily to withdraw toxic substances from the blood. Others have conceived the colloid as a sort of menstruum in which the real thyroid secretion was received and from which it might be withdrawn without visible change in the colloid itself. Still others have held the view that the colloid was the real secretion of the thyroid gland and that the normal mechanism of thyroid secretion was by this indirect route, first secreting into the centre of the follicle, and then withdrawing this ware-housed material, as functional needs required, by some unknown method and route.

The determination of the true significance of the colloid in the secretory cycle of the gland, and of the ways in which it is formed, and of its intracellular antecedents, is of fundamental importance in the physiology and pathology of the thyroid gland. The conviction that it is by this indirect method that the thyroid gland produces its internal secretion lies at the bottom of all of our more or less speculative interpretations of pathological conditions, and in view of the strong physiological evidence supporting this conviction few have had the courage to question its accuracy. Many authors have tried nevertheless to influence experimentally the rate of secretion in the gland, and to read in the changes so produced the true history of its secretory process. In this way many interesting facts have been discovered, which at present seem to some extent contradictory of one another, but which nevertheless must be found to be in accord when the true history of the process is revealed.

Our earliest knowledge as to the origin of the intrafollicular colloid of the thyroid gland is due to Biondi and Langendorff. Biondi ('89) showed that this substance was a true product of the secretory activity of the thyroid epithelial cells, inasmuch as he found globules of similarly staining substances in the cells themselves. He conceived the process of secretion as follows: the cells of the thyroid gland produce the colloid, since one can see in them little globules having the same microchemical reactions; the vesicle has a tendency to increase in size partly by

multiplication of the epithelial cells, partly by increase of the colloid; after filling itself the vesicle discharges into the nearest lymphatic vessel; finally the collapsed vesicle disposes itself in the form of a number of little acini which repeat the process.

Langendorff ('89) using the method of comparative study for the elucidation of the secretory process in the cells of the thyroid gland, reached conclusions which, in some respects, confirm and extend those of Biondi. He described two sorts of cells in the gland which he designated, respectively, principal cells, and colloid cells. The principal cells constituted the main mass of the epithelium. They were cylindrical or columnar cells, of variable height in different species and in different ages of the same animal species. They possessed a reticular protoplasm, with granules at the nodal points, and an oval or round nucleus situated at the basal end of the cell. Like Biondi he saw occasionally in these cells small hyaline spherules, but considered them to occur very rarely. The colloid cells differed from the principal cells by the hyaline, transparent appearance of their cytoplasm. This cytoplasm browned with osmic acid, and, in dyes, stained the same as the colloid content of the follicles. He found all grades of transition between the colloid cells and the principal cells. He regarded the colloid cells as elements engaged in the secretion of colloid but did not commit himself definitely to the opinion that, after a period of secretion, they might return to the state of the principal cells. He was likewise in doubt whether they degenerated or not after secretion.

V. Wyss ('89) studied the effects on the thyroid gland produced by poisoning with pilocarpine. He found in cats and dogs that the gland after pilocarpine was large, turgid, and filled with blood, and that the cells were larger, the nuclei less apparent. The free ends of the cells were prolonged into processes which were continuous with the colloid mass, and between these processes were brilliant spherules of apparently fluid nature.

Anderson ('94) confirmed V. Wyss' conclusions relative to the effect of pilocarpine on the gland, and studied the structure of the epithelial cells in young cats and rabbits at different periods of time after injections of pilocarpine. He described, in the

earlier phases of pilocarpinisation, the appearance of clear droplets in the cytoplasm, which collected at the free pole of the cell, to be extruded in the form of small droplets into the cavity of the vesicle. These, therefore, he regarded as the antecedents of the clear vacuoles of the margin of the colloid and on account of their lack of affinity for dyes, designated chromophobe secretion. A little later round, stainable droplets made their appearance in the free pole of the cell, which likewise migrated to the free border to be extruded into the lumen, constituting thus the chromophile secretion. He regarded the colloid cells of Langendorff as cells destined to degenerate. Thus, Anderson rejected the mode of secretion favored by Langendorff, and introduced the conception of a polyvalent secretion. His results, in general, are in more accord with those of Biondi than with those of Langendorff.

Hürthle ('94) in the same year studied the effects of reduction of thyroid tissue, and of bile retention, on the secretory processes of the gland. He found, as a result of each of these conditions, a great increase in the number of cells containing colloid spherules, which he therefore interpreted as an evidence of accelerated activity of the gland. On the other hand he recognized the occurrence of the Langendorff colloid cells to which he also ascribed secretory significance, and which he considered capable of transformation into principal cells.

Galeotti ('96) studied the thyroid glands of the turtle *Emys europaea*, under normal conditions, and after the injection of various products of metabolism. He described two sorts of secretion antecedents: fuchsinophile granules of nuclear origin, previously undescribed, and droplets of colloid like those described by Biondi, Anderson, and Hürthle. These two secretion antecedents varied independently of one another under the experimental conditions employed.

Following Galeotti a number of different observers using his methods studied the thyroid gland under different experimental and pathological conditions, confirming his results as to the double character of the thyroid secretion and the independent variation of the two sorts of secretion. Among these may be

mentioned Tiberti, and Ciulla. The latter identifies the fuchsinophile granulations of Galeotti with the chromophobe secretion of Anderson, the plasmosomes with the chromophile secretion of the same author.

Lobenhoffer ('09) studied human thyroid glands, both normal and pathological, in material fixed in formol Müller, and stained in anilin acid fuchsin. He found, in his preparations, the cells containing in widely varying amounts spherical fuchsinophile granules about the size of the granules of eosinophile leucocytes. Sometimes these granules formed a narrow row along the margin of the cell, and sometimes very small granules were found actually in the margin of the colloid. These granules he regarded as the antecedents of the thyroid secretion, interpreting the varying contents as indicating different phases of secretory activity.

As a result of the work of these observers we have to consider the following structures, in connection with the secretory activity of the thyroid cells, as possible intracellular secretion antecedents:

1. Spherules of colloid, described by all observers except Lobenhoffer.

2. Vacuoles containing a colorless unstaining fluid substance described by Anderson as chromophobe secretion, and interpreted by him as the antecedent of the content of the vacuoles seen in the margin of the colloid.

3. Colloid occurring as a diffusely distributed substance in the cytoplasm of the so-called colloid cells of Langendorff.

4. The fuchsinophile granules of Galeotti.

5. The fuchsinophile granules of Lobenhoffer.

Recent work by O. Schultze, and Mawas has helped to reduce the number of supposed secretion antecedents in the preceding list by demonstrating the presence in the thyroid epithelial cells of numerous mitochondria, usually filamentous, and oriented in the direction of the main axis of the cells. There seems to be little doubt that the fuchsinophile granules of Lobenhoffer are in reality mitochondria, rather imperfectly preserved. To this category belong also in part at least the fuchsinophile granules of Galeotti, Tiberti, and others. Possibly however, a part of these

granules are of another nature, since I have shown that in hyperplastic glands of the opossum and in human glands from cases of exophthalmic goiter, non-mitochondrial fuchsinophile granules occur. These will require further discussion when the secretory by-products are considered.

With the exception of Hürthle, Langendorff, and Schmidt, practically all observers agree that the colloid cells of Langendorff are cells in the last stages of cytomorphosis. The perfect gradation between these cells and the so-called principal cells on the one hand and the obviously degenerating cells of the follicle on the other hand leaves little doubt of their significance. The changes in the nucleus, the disappearance of mitochondria, and, in many cases, the visible disintegration of the cytoplasm, or desquamation of the cell, all point to the correctness of this conclusion.

Thus by elimination we arrive at the conclusion that the only secretory antecedents thus far demonstrated in the thyroid epithelial cells which may be considered to be normal products, are the colloid globules of Biondi, and Hürthle, to which belong also the chromophile granules of Anderson, and the so-called chromophobe secretion of Anderson. It is necessary, therefore to examine in greater detail the occurrence of these products in the thyroid epithelial cells, with the object of determining whether they are actually related to the formation of intrafollicular colloid, whether they are sufficient to account for the physiological activity of the gland, and what indications they afford of the rate of formation of the intrafollicular colloid.

Hürthle found that, when the thyroid tissue was reduced by the removal of the whole of one lobe and two-thirds of the other, in many places in the gland the epithelial cells contained droplets of substance which was sharply defined by its staining reaction from the surrounding protoplasm, but agreed in all respects with the colloid contained in the follicular lumina. Similar results he obtained by ligating the common bile duct and the thoracic duct simultaneously. In these glands also he found the lymphatic vessels much dilated and filled with strongly staining colloid substance without admixture of formed elements. He con-

sidered two possible explanations of this phenomenon, namely, that it was due to lymphatic obstruction, and that it was due to accelerated activity of the gland, and decided in favor of the latter alternative because ligation of the thoracic duct alone produced no such changes in the gland.

Langendorff (*loc. cit.*) on the other hand, while admitting the occasional occurrence of colloid droplets in the cells, did not consider them of much significance from the secretory standpoint because of their extreme rarity. Anderson also saw them, not in the normal cell, but as a result of prolonged pilocarpinisation of the animal. Schmidt could find no effect on the structure of the epithelial cells as a result of pilocarpine injections, and attached more importance to the colloid cells as an indication of secretory activity. Bensley ('14) on the contrary, in studying the involution of the hyperplastic gland of the opossum produced by the administration of iodides, found that the cells of the gland practically all contained globules of colloid, and that they could be seen discharging it into the lumen, while colloid cells were almost completely lacking. In this case the restoration of the intrafollicular colloid was wholly by the formation of intracellular globules which discharged into the lumen. The process however was an extremely slow one; after seventeen days, though practically every cell contained a globule of colloid, as large as, or larger than the nucleus, there was little intrafollicular colloid, and at the end of twenty-four days of daily administration of iodides the condition was but slightly advanced; intracellular colloid remained about the same as in the preceding case but the follicular colloid was somewhat increased. Recent experiments on the hyperplastic glands of the opossum have amply confirmed these results; iodine administered daily to the animal with a hyperplastic gland produces a gradual involution marked by the slow accumulation in the cells of colloid droplets, usually a single drop to a cell, and the ultimate discharge of these into the newly formed lumen. We may consider it proven therefore that the production of colloid under certain special conditions is by this method.

This conclusion raises the question whether the production of colloid under normal conditions of functioning is by the same method, and, if so, what are the implications of this fact from the standpoint of secretory rate?

Hürthle claimed that the formation of colloid droplets in the epithelial cells of the thyroid gland was one of the ways of formation of colloid and that their presence was an indication of accelerated thyroid activity. Langendorff pointed out that they were extremely rare, and therefore could not have the secretory importance claimed by Hürthle. That Langendorff's contention in this respect is correct will readily be admitted. Indeed, one may search complete series of sections of small thyroid glands, and thousands of sections of larger ones without finding in them a single droplet of intracellular colloid. In six thyroid glands of man obtained at autopsies on executed criminals, and examined by the writer, only one contained epithelial cells with colloid droplets in them. In pathological glands from cases of exophthalmic goiter, simple colloid goiter, and colloid adenoma, on the other hand, they occurred with variable frequency. In the one normal gland that contained them the colloid drops occurred with great frequency. For the most part they were placed not at the free margin of the cell, but deep in the protoplasm, often alongside of the nucleus, and in many cases several drops formed a row extending from this deeper location to the free border. In many follicles, however, the colloid droplets occupied the tips of the epithelial cells, and in others the colloid masses inside the follicle could be seen to be made up of a cluster of small droplets, apparently derived from different cells, which had failed to fuse with one another inside of the follicle. This gland also contained an unusual number of colloid cells of Langendorff.

The obvious participation of these intracellular colloid droplets in the replenishment of the intrafollicular colloid, on the one hand, and the slowness of this process demonstrated by experiment, and the rarity of the occurrence of such droplets under normal conditions, on the other hand, suggest the following possibilities, which, however, are not, as will appear more clearly later, mutually exclusive: (1) the formation of colloid is an inter-

mittent function of the thyroid cells; (2) there are other, at present unknown mechanisms for the formation of colloid, correlated with droplet formation, but able to proceed without it; (3) the secretion of colloid into the gland lumen is an accessory and not the primary function of the epithelial cells of the gland.

For the reasons mentioned above, it is apparent that the formation of colloid droplets in the cell, at least, is an intermittent function. It is possible, however, that in addition to this mode of formation of colloid there is a slow and continuous production of colloid at the free margin of the cell unaccompanied by the formation of visible secretion antecedents in the cytoplasm, and it may be that this latter is the main method of production of intrafollicular colloid, the droplet method representing some upset of secretory equilibrium which results in the accumulation of the product of secretion in the cell, instead of the lumen. That this hypothetical upset is of the nature of an acceleration of the secretory rate is, however, excluded by the fact that we often see the droplet formation in the greatest abundance in adenomata the stroma of which is in an advanced state of hyaline degeneration, and in which, therefore, there can be no question of accelerated secretion rate. Histologically considered such a conception of the process of secretion in the thyroid gland must remain hypothetical, since it is incapable of objective proof.

The third possibility, namely, that the secretion of colloid into the gland lumen is an accessory and not the primary function of the epithelial cells, though correlated intimately with this primary function, would, if established, explain and include all of the facts. Such a theory to be accepted, must account for the irregular occurrence of droplets, for their formation in the interior of the cell rather than on either of the free surfaces, and for their increase under iodin or thyreoglobulin administration, and under the experimental conditions of Hürthle. It involves the assumption of a more remote antecedent of the secretion than the colloid droplets of Hürthle.

In my studies of the thyroid glands of various mammals, I have been struck with the frequent occurrence, particularly in the cat, dog and opossum, of vacuoles with unstainable con-

tents, rather irregular in shape, occurring in the base of the cell, and with the frequent occurrence in the cells of hyperplastic human glands from cases of true exophthalmic goiter of droplets of material staining like colloid located similarly in the extreme bases of the cell near the capillary net. Ferguson ('11), also, has described the occasional occurrence in the thyroid gland of elasmobranch fishes of cells presenting in their basal ends a ragged and rodded appearance which he interprets as due to secretion storage for direct export to the vascular channels.

A group of opossums kept under observation under various experimental conditions during the past winter have furnished material in which, by reason of the fact that these vacuolar substances in the cell were unusually increased in amount, it was possible to study their variation and to develop a technique for staining of their contents. One group of these animals was kept for a period of three weeks on a dietary consisting of beef, bread and fat, egg, bread and fat, or cheese, bread and fat, just sufficient to maintain constant weight. In another group the diet was so regulated that with constant bread and fat content there was a progressive increment of meat fed to the successive members of the series. In all of the animals thus kept on a controlled diet, the thyroid cells contained such basal vacuoles, and in two of the animals of the second series, namely those which received, respectively, twice and two and a half times the normal meat ration, the material of this sort comprised fully half of the cell contents.

The fixation of the material is of considerable importance in the study of these vacuolar substances, because the contents are so dilute that they may be precipitated in an invisible form on the protoplasmic strands which wall the vacuoles. Formalin zenker, however, was found to precipitate the contents in the form of a thin gel sometimes filling completely the space of the vacuoles, sometimes containing small vacuoles from contraction in fixation. Staining however was difficult, because the material stained with the usual dyes in the same way as the protoplasm. With Mallory's connective tissue stain, however, it could be seen that the vacuoles had vaguely staining contents, but, since the

protoplasm also stained bluish after formalin zenker fixation, it was difficult to define accurately the limits of the vacuoles, and after fixation in ordinary Zenker's fluid the vacuoles did not stain at all. Accordingly the indication was to find some stable stain which would stain the protoplasm diffusely, and then to stain the secretion a contrast color. For this purpose brasilin in phosphotungstic acid solution was found to be effective. The solution is prepared as follows:

Phosphotungstic acid.....	1.0 g.
Distilled water.....	100.0 cc.
Brasilin.....	0.05 g.

The brasilin is first dissolved in a small quantity of distilled water by the aid of heat and added to the phosphotungstic acid solution. Ripening may be accelerated by the addition of 0.4 cc. of hydrogen peroxide, or of a few drops of a solution of soluble molbydlic acid. The solution deteriorates with age and should not be used after three days.

Sections of thyroid glands which have been fixed in formalin zenker, fastened to slides by the water method (if albumen is used it should be very small in amount) are passed through toluol, absolute alcohol, to water, iodised, and placed in the staining solution from one to several hours. The sections are then washed in water and placed for one to five minutes in the following solution:

Phosphomolybdic acid.....	1.0 g.
Wasserblau.....	0.2 g.
Water.....	100.0 cc.

Then wash rapidly in water, dehydrate in absolute alcohol, clear in toluol, and mount in balsam.

In the preparations so stained with brasilin and wasserblau the cytoplasm stains pink to lilac, the nuclear chromatin, deep red, and the contents of the vacuoles sky blue, as shown in Fig. 1. The colloid droplets of Hürthle stain deep blue or deep red according to the concentration of the gel which composes them, which determines the diffusion rate of the dyes employed.

It must not be supposed that the technical difficulties of studying this intracellular product are wholly overcome by the method just described. When the material is large in amount the method is very satisfactory, but the intensity of the protoplasmic staining is not sufficient to define the material sharply when it is small in amount. Under these circumstances, a brief mordanting of the section, before staining, in a fresh solution of ammonium stannic chloride will improve the contrast staining, but will detract greatly from the transparency and beauty of the preparation.

The examination of the sections of the experimental series referred to above, and of a number of normal glands from animals killed as soon as obtained, reveals the presence in all, although in highly variable amounts in the individual members of the series, of a new secretion antecedent. This substance is in the form of vacuoles, occurring exclusively in the outer pole of the cell, which contain a dilute solution similar in its properties to the colloid of the follicular lumen, differing from the latter only in density. There are even in this substance clear vacuoles due to shrinkage in fixation, like those seen in the colloid of the lumen.

In two members of the experimental series, this substance is present in such amount that it fills quite half the cell. In these cases the cell presents an appearance comparable to that of the secreting cells of an exocrine gland like the pancreas, with the exception that the hylogens are in dilute solution in fairly large vacuoles instead of in the form of granules, and they are in the basal end of the cell instead of the free end. In other words these cells exhibit the ordinary picture of a secreting cell with stored secretion antecedents, but with reversed polarity.

Figure 1 shows an acinus from one of these glands. The cells are cylindrical in shape with a spherical nucleus placed rather nearer to the free end of the cell than to the base. The base of the cell is filled with sky-blue stained material contained in vacuoles separated from one another by thin sheets of cytoplasm containing mitochondrial filaments. The free pole of the cell directed towards the lumen is finely granular and stained a bluish-pink color. It contains none of the blue staining vacuolar

material, and consists solely of cytoplasm containing crowded mitochondrial filaments. In two cells of this figure small globules of colloid may be seen, in one case alongside of the nucleus, and in another in the apical cytoplasm.

In some of the thyroid glands obtained from opossums recently captured, consisting of fairly large follicles well filled with colloid, the epithelial cells appeared uniformly vacuolated, but when the preparations were stained with brasilin and wasserblau the vacuoles in the outer ends of the cells were found to be filled with blue staining material, those in the inner ends with unstainable material.

Three possible interpretations of the presence of this material suggest themselves: first, that it is a pathological product representing cytoplasmic degeneration, or imbibed serous fluid, or simple edema; second; that it is colloid in process of resorption by a transcellular route; third, that it is a true secretion antecedent representing material formed in the base of the cell for the purpose of direct transport into the vascular channels.

The fact that every cell of the gland contains the material, that it is present in some degree in all opossum thyroid glands, and that there are no other evidences of degeneration, such as changes in the nucleus or in the mitochondria, or in the intra-lobular connective tissue excludes the first possibility from consideration.

Opposed to the second of these hypotheses is the fact that only very exceptionally is this material found in the pole of the cell in contact with the follicular content, and then only when the cell is so loaded with the secretion that it is comparable in appearance to a parotid gland cell filled with zymogen granules. It might be possible to assume that the droplets of colloid occasionally seen in the cell are on the way out rather than proceeding towards the lumen. The evidence from the glands which are being reverted by iodine is, however, strictly opposed to this hypothesis, since a progressive increase in colloid in these cases has been demonstrated in an experimental series taken at different intervals of time and this increase is associated directly with colloid droplet formation and extrusion into the lumen. It is

conceivable, of course that the droplets of colloid are of two sorts, those destined for the follicular content, and those on their way to the base of the cell for secretion into the vascular channels of the gland. Opposed to this assumption is the fact that in entire glands, in the cells of which there is an abundance of the basal vacuolar substance there may be found not a single droplet of colloid of the dense type, and that the free poles of all the cells may be wholly free from products of secretion except where the crystals, of protein nature, demonstrated in a former article, project into this pole. Furthermore, in hyperplasia of long standing, in which there is practically no intrafollicular colloid, a large content of the new secretion in the form of small vacuoles distributed throughout the outer pole of the cell, may be present.

We are therefore forced to accept the third hypothesis which, physiologically considered, is the more attractive, inasmuch as it permits of harmonizing the various facts under a single hypothesis, namely that the secretion collected in the outer pole of the thyroid cell is destined to direct transport into the vascular channels, and that the thyroid cell represents a true reversal of polarity in accord with its endocrine function.

In addition to the facts mentioned above which point strongly to the correctness of this hypothesis, it may be pointed out that in exocrine glands fat droplets which are deposited in the secreting cells practically always make their appearance at the anti-secretory pole of the cell; this is the case in the pancreatic cells and in the chief cells of the gastric glands. The location of the fat deposits in the thyroid gland also is at the pole which according to the hypothesis here supported is the anti-secretory pole of the cell, namely the free end of the cell next the colloid.

We may assume therefore that the thyroid gland as all physiological and clinical experience indicates, prepares and secretes into the vascular channels of the gland a secretion, and that this secretion is formed in the outer pole of the cell, and excreted from it directly under normal conditions of functioning without passing by the indirect route through the follicular cavity.

It is necessary, however, under this hypothesis to explain the occurrence of intrafollicular colloid, and its variability in different members of a species and under different experimental conditions. In my recent studies on the changes in the hyperplastic gland of the opossum and its changes under domestication, I have shown that all the stored colloid may be withdrawn from the gland in a short period, and that the gland will maintain for a period of several months a condition in which little visible colloid is present in the gland, but, as Marine previously demonstrated in the dog, if iodine be administered the vesicles are reformed, and filled with dense colloid. In the opossum this colloid makes its appearance first deep in the thyroid cells, but migrates to the free surface and is there discharged into the lumen. I have also found in the study of many glands from cases of Basedow's disease that the few colloid droplets which are present are very frequently found at the level of the nucleus, or even in the base of the cell. These facts indicate that in addition to the direct mode of secretion there is an indirect mode, which consists in the condensation of the secretion into the form of droplets having a high content of solids, and the extrusion of these droplets into the follicular cavity. These droplets are formed in the same zone of the cell as that in which the primary or direct secretion is formed, and it is probable that they are formed at the expense of the latter.

The readiness with which the thyroid gland undergoes hyperplastic change, its responsiveness to iodine administration, as demonstrated by Marine and his co-workers, the ease by which it may be modified structurally by dietary conditions as shown by the work of Reid Hunt ('11), Marine, Chalmers Watson ('07), Tanberg ('00), and Missiroli ('10) and confirmed by my recent studies on the relation of diet to hyperplasia in opossums under domestication, confirm the conclusion that there is a delicate adjustment between the functioning of the thyroid gland and general body conditions, though at present we do not know the means by which this adjustment is mediated. This being the case it may be assumed that only when this adjustment is disturbed so that the rate of secretion is in excess of body needs, the indirect

mode of secretion comes in, and the product of secretion is condensed and stored in the intrafollicular cavity. It is conceivable, of course, that other factors than excess of production over functional needs might bring about this result, as, for example, an agent inhibiting direct export from the cell, or mechanical interference with the outflow from the cells. The latter influence is well illustrated in the colloid adenomata where, notwithstanding the fact that the stroma may be hyaline, the cells contain abundant colloid spherules, and thus give, according to the old criterion of Hürthle, the impression of high secretory activity. According to my hypothesis of thyroid secretion, this condition would represent a slow secretory activity of the epithelium of the tumor, all of the energy of which is, however, devoted to storage, since direct export by way of the vascular channels is impossible. This may explain the difference noted by Marine between the hyperplastic gland and the adenoma as to susceptibility to influence by iodine. The hyperplastic gland, whether its activity be high or low, is exporting its product directly. Iodine whether by accelerating the activity of the gland and so producing a condition of physiological saturation with thyroid products, or by actually inhibiting the export of material from the cell, causes the cell to reverse its processes, and store it in the follicular cavities. The adenoma is already storing all of the product which the vascular conditions and its specific cell equilibrium permit it to form, and so the process can not be influenced by iodine.

According to this conception of thyroid secretion the colloid in the thyroid vesicles is *per se* no measure of the activity of the gland at the moment of observation, though its consistence and its qualities may offer valuable indications of the capacity of the thyroid cell for normal storage. The colloid in fact may be the product of a storage phase which preceded the examination of the gland by a considerable period of time, since it is necessary to assume the resorption of this material only under the conditions where the normal direct secretory activity of the gland is insufficient to meet the functional demands. Accordingly, also, lack of colloid in the gland does not necessarily mean depression of the gland activity below the normal rate at the time of observation, though it probably does mean that there is such a

depression of physiological efficiency or has been at some previous time, and either that the gland has not risen above the level of secretory rate needed for direct export, or that there has been a failure of the normal mechanism of regulation. My observations on the hyperplastic glands of opossums by means of the methods described in this paper have shown that hyperplastic glands which appear almost identical histologically may yet differ markedly in the amount of these intracellular secretion antecedents which they contain, and thus, probably, in secretory potential.

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EXPLANATION OF PLATE

1 A group of follicles from the thyroid gland of the opossum, fixed in formalin zenker, stained with brasilin-wasserblau. $\times 1050$. In the outer poles of the cells a material differentially stained, similar to the intrafollicular colloid. In two cells droplets of colloid destined for storage.

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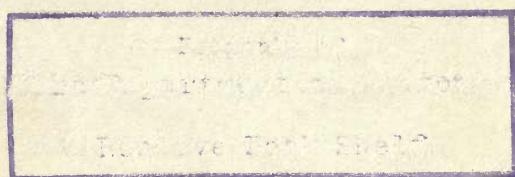
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